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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,827	01/31/2005	Simona Jevsevar	LB/G-32992A/LEK	2050

7590 06/09/2009

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
06/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/522,827	**Applicant(s)** JEVSEVAR ET AL.	
	Examiner XIAOZHEN XIE	**Art Unit** 1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 April 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *29 April 2009*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *1,4,6,8-11,13,14,20-22 and 25*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *2,3,5,7,15-19 and 26*.
   Claim(s) withdrawn from consideration: *24*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646

Continuation of 11. does NOT place the application in condition for allowance because:

The claims have been ameded to change the dpendency of claim 4, and to correct a typographical error in claim 15.

Applicant argues that the specification fully describes how to modify a DNA sequence coding for hG-CSF defined by SEQ ID NO: 3; and the claims calls for making modifications to particular segments of the gene. Applicant argues that as one example of a modified gene in accordance with claim 2, the specification details a step by step construction of an optimized hG-CSF gene, Fopt5 (SEQ ID NO: 1). Applicant argues that with knowledge of this inventive modified sequence, many other variants within the scope of the claim 2 sequence become apparent, as long as one or more of the recited modifications are made in the identified segments of SEQ ID NO: 3. Applicant argues that it would readily be within the ordinary skill of one in the art to produce such variants, based on Applicants' disclosure. Applicant argues that the rejection of claim 2 is based on improper attempt to draw subject matter from claim 4 into claim 2 (claim 4 recites a limitation of the expression level). Applicant argues that claim 2 does not specify an expression level of at least about 50%, instead, claim 2 merely calls for a modified DNA sequence coding for hG-CSF, with specific modifications in Segments I-IV as claimed and taught in the specification. Applicant further argues that the disclosed example, Fopt5, is sufficient disclosure for the claimed genus.

Applicants' argument has been fully considered and has been found partially pursuasive with regard to the rejection under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

The claims that are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, include claims 3, 19 and 26.
These claims recite functional limitations for the variants, i.e., encoding a biologically active G-CSF, and having a protein expression level in E. coli of at least 50%. Although the specification describes on pages 9-10 the codon changes at specific positions which are encompassed in the genus of independent claim 2, however, there is no sufficient written description for those variants that meet the functional limitations as recited in the instant depending claims. Applicant has not provided sufficient identifying characteristics, nor structural and functional correlations, nor representative number of species, that conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the genus. Further, the variants contain moifications not just limited in the four segments, because the use of the open-ended transitional phrase "comprising".

Applicants' argument with regard to the rejection under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, has been fully considered, but has not found to be pursuasive for reasons of record set forth in the previous office action.

Independent claim 2 is very broad encompassing nucleotide or codon changes not only in the four segments with the recited E. coli rare codon and GC rich regions, but also include other changes throughout the gene, since the claim uses the term "comprising". The claim does not even limt these variants having any biological/functional activity. While the specification describes as one example, a synthetic gene (Fopt5) coding for a biologically active hG-CSF (SEQ ID NO: 1), which, when expressed in E. coli, yields hG-CSF more than 40% in total protein. The specification, however, has not provided sufficient guidance as to how to make and use the genus. Given the broad scope of the genus, these variants may not have any biological activity. Obviously, it requires undue experimentation to determine whether these variants are useful and what activity/function these variants have. Further, as stated previously and supported in the Krishna reference, even changes only occurred in the four segments with the recited changes, the variants may not improve the expression yield as the exemplified Fopt5 or as recited in the depending claim. Without detailed guidance, one of skill in the art would evaluate an extremely large number of non-exemplified synthetic G-CSF genes to determine how to make and use the invention as broadly claimed.